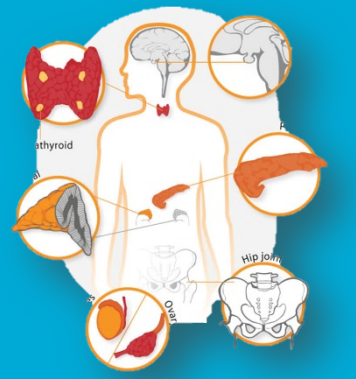
[lecture 5]

Addison's Disease



Endocrine system

Biochemistry Team

Teams

The Objectives

- To identify different causes of primary adreno-cortical hypofunction (Addison's disease)
- To identify secondary causes of adreno-cortical hypofunction
- To understand the diagnostic algorithm for adreno-cortical hypofunction
- To understand the interpretation of laboratory tests of adreno-cortical hypofunction

Red = Import-ant

Blue = explain

Green = addition notes

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Mind Map

Mind Map

- Background
- Steroid Hormone Synthesis
- The renin-angiotensin system
- Causes of adrenocortical hypofunction
- Signs and symptoms of primary adrenal failure (Addison's disease)
- Investigation of Addison's disease (AD)

Background

Anatomy and Histology of adrenal gland:

-The adrenal gland is situated on the anteriosuperior aspect of the kidney and receives its blood supply from the adrenal arteries.

-The adrenal gland consists of two distinct tissues of different embryological origin, the outer cortex and inner medulla.

The adrenal cortex comprises three zones based on cell type and function:

- Zona glomerulosa :The outermost zone → aldosterone (the principal mineralocorticoid).
- Zona fasciculata → glucocorticoids – mainly cortisol (95%)
- Zona reticularis → Sex hormones

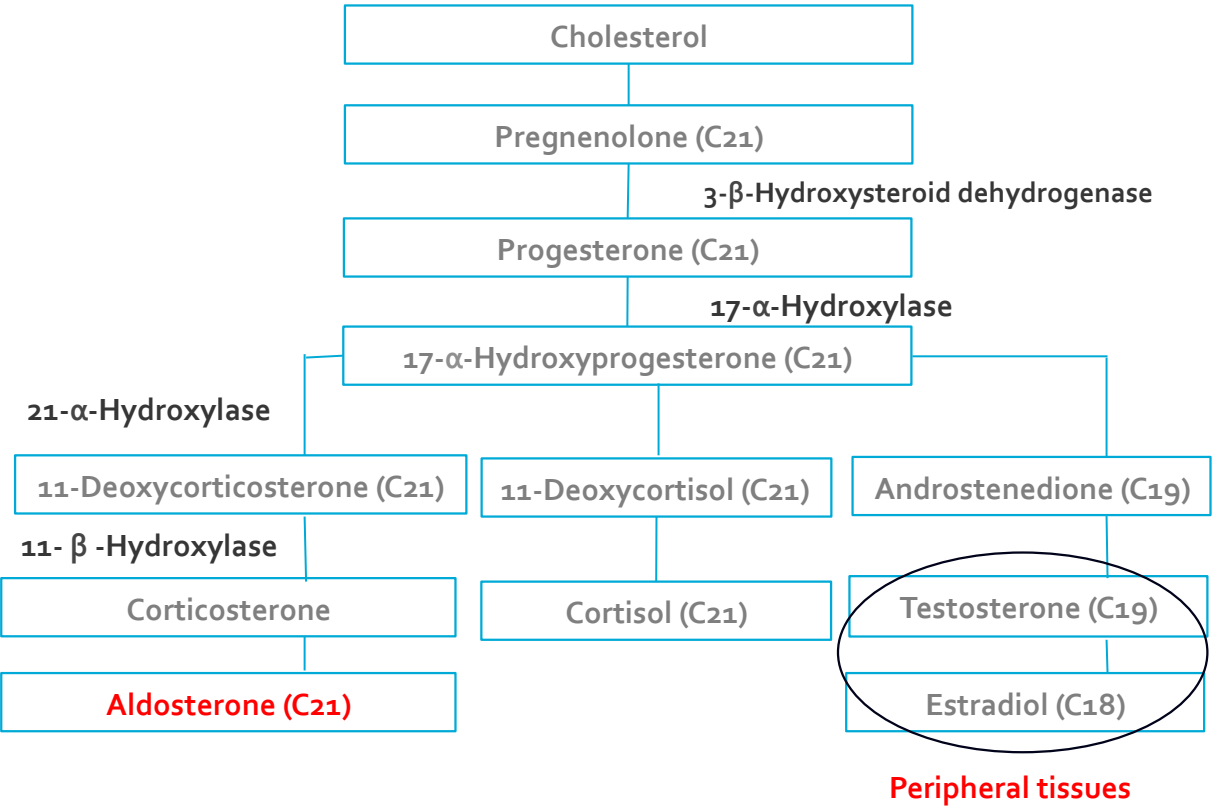
Aldosterone Hormone:

-The principal physiological function of aldosterone by acting on the distal convoluted tubule of kidney is to:

- **conserve Na^+, mainly** by facilitating Na^+ reabsorption. (↑ sodium and water reabsorption)
- **reciprocal K^+ or H^+ secretion**.(↑ potassium excretion)

-aldosterone is a major regulator of water and electrolyte balance, as well as blood pressure .

Steroid Hormone Synthesis

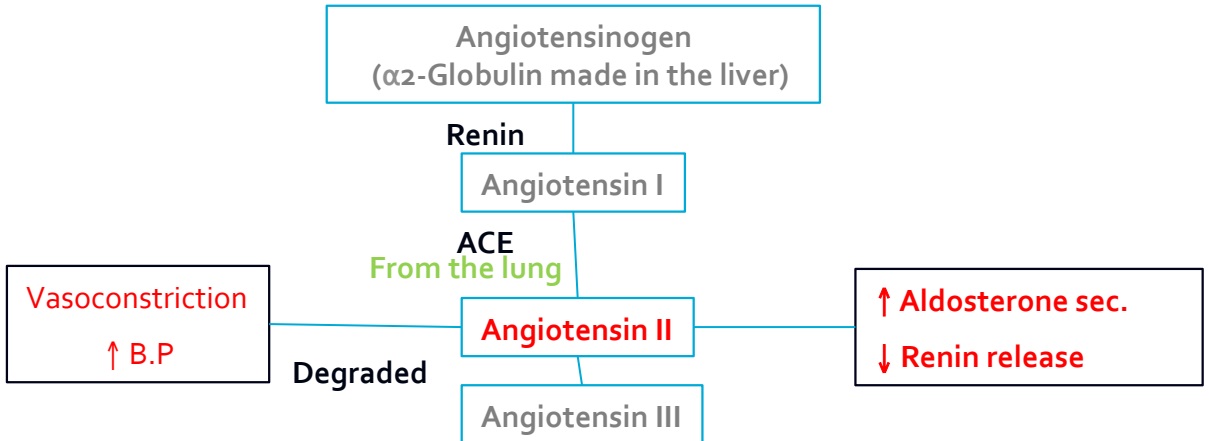


The renin-angiotensin system

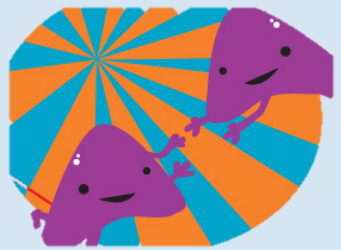
*Renin-Angiotensin system is the most important regulatory mechanism for aldosterone secretion ,It is involved in B.P. regulation.

*Renin: a proteolytic enzyme produced by the juxtaglomerular cells of the afferent renal arteriole, Sensitive to B.P. changes through baroreceptors.

*released into the circulation in response to :
1. ↓ circulating blood volume. 2. ↓ renal perfusion pressure. 3.loss of Na^+.



Adrenocortical hypofunction

	primary	secondary
Causes	Primary destruction of adrenal gland: • Autoimmune • Infection, e.g., tuberculosis • Infiltrative lesions, e.g., amylodosis • There will be ↑ ACTH , ↓ Cortisol and aldosterone	Secondary to pituitary disease: • Pituitary tumors • Vascular lesions • Trauma • Hypothalmic diseases (tertiary) • Iatrogenic (steroid therapy, surgery or radiotherapy) • There will be ↓ ACTH , ↓ cortisol only • aldosterone will be normal because it's secretion doesn't depend on ACTH, it depends on ACTH in the formation and small amount of ACTH will be enough, but not enough for the secretion of cortisol.
Signs and symptoms	The symptoms are precipitated by trauma, infection or surgery: • Lethargy, weakness, nausea & weight loss. • **Hypotension** especially on standing (postural) • **Hyperpigmentation** (buccal mucosa, skin creases, scars) • Deficiency of both glucocorticoids and mineralocorticoids • **Hypoglycemia**, ↓ Na^+, ↑ K^+ and raised urea Increase urea because of hypovolemia • Life threatening and need urgent care. -**Hyperpigmentation** occurs because melanocyte-stimulating hormone (MSH) and (ACTH) share the same precursor molecule, Pro-opiomelanocortin (POMC). -The anterior pituitary POMC is cleaved into **ACTH, γ-MSH, and β-lipotropin**. B-lipotropin help in lipolysis and help in melanin formation -The subunit ACTH undergoes further cleavage to produce **α-MSH**, the most important MSH for skin pigmentation.	In secondary adrenocortical insufficiency, skin darkening does not occur. 

Adrenocortical hypofunction

Investigation

Screening

- The patient should be hospitalized
- Basal measurement of: Serum urea, Na^+, K^+ & glucose ,Serum cortisol and plasma ACTH
- Definitive diagnosis and confirmatory tests should be done later after crisis.
- Normal serum cortisol and UFC (urinary free cortisol the active form) does not exclude AD.
- Simultaneous measurement of cortisol and ACTH improves the accuracy of diagnosis of primary adrenal failure:

Low serum cortisol (<200nmol/L) , **High plasma ACTH** (>200 ng/L)

- **Low serum cortisol with low plasma ACTH**.
- No response to short synacthen test: Adrenocortical cells fail to respond to short ACTH stimulation

Confirmatory Tests

:-Short tetracosactrin (Synacthen) test (Short ACTH stimulation test)

- Measure basal S. cortisol (serum cortisol)
- Stimulate with I.M. synthetic ACTH (0.25 mg)
- Measure S. cortisol 30 min after I/M injection
- Normal: **↑ of S. cortisol** to >500 nmol/L
- **Failure of S. cortisol to respond to stimulation**, confirm AD addison's disease .

- Abnormal results:
1.emotional stress. Because it increase cortisol level
2.glucocorticoid therapy
3.estrogen contraceptives } Both suppress the adrenal gland

-Depot Synacthen test :
1. Measure basal S. cortisol
2. Stimulate with I.M. synthetic ACTH (1.0 mg) on each of three consecutive days
3. Measure S. cortisol at 5 hours after I.M. injection on each of the three days

-Addison's disease: **No rise of S. cortisol** >600 nmol/L at 5 h after 3rd injection.
-Secondary AC: **Stepwise increase in the S. cortisol** after successive injections

-Limitations:
1.Hypothyroidism: Thyroid deficiency must be corrected before testing of adrenocortical functions
2.Prolonged steroid therapy

Others

1. Adrenal antibodies :Detection of adrenal antibodies in serum of patients with autoimmune Addison's disease
2. Imaging (Ultrasound/CT) : for adrenal glands for identifying the cause of primary adrenal failure

1. Insulin-induced hypoglycemia: Adrenal failure secondary to pituitary causes. It will not respond to the test because there is no ACTH
2. MRI for pituitary gland

summary

- Renin-Angiotensin system is the most important regulatory mechanism for aldosterone secretion
- Causes of primary adrenal insufficiency Autoimmune,Infection, e.g., tuberculosis andInfiltrative lesions, e.g., amylodosis
- Causes of secondary adrenal insufficiency are Pituitary tumors, Vascular lesions ,Trauma,Hypothalmic diseases (tertiary)
- and Iatrogenic (steroid therapy, surgery or radiotherapy.
- In secondary adrenocortical insufficiency, skin darkening does not occur.
- In primary adrenal insufficiency Low serum cortisol, High plasma ACTH but in secondary Low serum cortisol with low plasma ACTH.
- Short tetracosactrin (Synacthen) test (Short ACTH stimulation test) is confermatory test for both primary and secondary adrenal insufficiency but in primary
- there is no rise in S.cortisol and in case of secondary there is Stepwise increase in the S. cortisol

Test your knowledge ..!

1:The cause of hyperpigmentation in the primary adrenocortical insufficiency is?
A: ACTH stimulates melanin production
b: ACTH and MSH share the same precursor
c: ACTH increase the sensitivity of MSH receptor.

2: A patient injected with synthetic ACTH, then after 30 minutes we measured his serum cortisol and it was normal this result indicates:
A: primary addison's disease
b: secondary addison's disease

3: to confirm secondary addison's disease we inject the patient with synthetic ACTH for …. days, on each day we measure his serum cortisol after …… :
A: 3 … 5 hours
b: 5 … 3 hours
C: 3 … 5 minutes

4: the response in case of patient with secondary addison's disease injected with insulin is:
a: increase the cortisol level to compensate hypoglycemia
b: hypoglycemia becuase the pituitary gland loss the compebsatory mechanism
C: hypoglycemia because there is destruction of the cells of the adrenal gland

1.B
2.A
3.A
4.B

Biochemistry
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